

# Suggestions for use of hypertonic saline solution with hyaluronic acid in cystic fibrosis patients

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**Abstract.** The use of hypertonic saline (HS) is recommended in children (>6y) and adults with CF. The addition of HA is beneficial in CF patients who have previously shown poor tolerance to HS and may add an important anti-inflammatory effect to this treatment. ([www.actabiomedica.it](http://www.actabiomedica.it))

**Key words:** hypertonic saline, hyaluronic acid

## Introduction

The pathogenesis of lung disease in cystic fibrosis is characterised by decreased airway surface liquid volume and subsequent failure of normal mucociliary clearance. Therapies acting against airway mucus in cystic fibrosis include aerosolized hypertonic saline. It has been shown that hypertonic saline possesses mucolytic properties and aids mucociliary clearance by restoring the liquid layer lining the airways. Recent clinical and bench-top studies are also beginning to broaden the view on the beneficial effects of hypertonic saline, which now extend to include anti-infective as well as anti-inflammatory properties (1). This article reviews the current indications for the use of hypertonic saline and hypertonic saline with hyaluronic acid in CF patients.

## Discussion

In clinical trials, inhaled hypertonic saline has been shown to improve lung function and decrease the frequency of exacerbations in adults and older children with CF.

Riedler and colleagues (2) performed a crossover trial in 10 adolescents with an exacerbation of their CF

lung disease. Prior to a session of physiotherapy, subjects were randomized to inhale either 6% hypertonic saline or a normal saline control. On the following day, the alternate solution was inhaled prior to an identical physiotherapy session. Significantly more sputum was expectorated after hypertonic saline than control ( $p = 0.006$ ). Subjects also rated how much clearer their chest felt after physiotherapy, with significantly better scores when hypertonic saline had been used ( $p=0.04$ ) – an effect also reported in adults and children. Eng and colleagues (3) randomized 52 children and adults with CF to twice-daily inhalations of 6% hypertonic saline or a normal saline control. Within two weeks, the average FEV1 improvement among those taking hypertonic saline was 15% (SD 16), while the control group improved only 3% (SD 13) ( $p = 0.004$ ). Two weeks after ceasing the inhalations, there was no significant difference in lung function.

A benefit in lung function appears to be maintained with long-term use. In a randomized trial which enrolled 164 adults and children with CF, the hypertonic saline group maintained significantly higher lung function across the 48-week follow-up period (4). Other clinical benefits were: a reduction in the frequency and duration of exacerbations, and fewer days missed from usual activities due to the disease.

These benefits were accompanied by an improvement in several domains of quality of life. There was also close monitoring of sputum samples throughout the trial to check for any adverse effects on acquisition of organisms, organism density and inflammation. An often overlooked benefit was that patients in the active arm of the study rated their ease of clearing sputum as significantly greater at the end of the trial.

Use of inhaled HTS during hospitalisation for acute exacerbation of CF was not associated with FEV1 improvement, additional weight gain or increased time to next admission over standard treatment in this retrospective study (5).

No study has identified a subgroup of CF patients that responds particularly well to hypertonic saline therapy. For example, in the long-term trial (4), the effect of hypertonic saline on exacerbations did not differ significantly between users and non-users of physiotherapy, between subjects with mild or severe lung function impairment, nor between users and non-users of recombinant human deoxyribonuclease (rhDNase). So, some authors extend the recommendation of this therapy to all those people with CF who find it tolerable (6).

These controlled trials of hypertonic saline only recruited participants older than 6 y of age.

So its use as a therapy in early CF lung disease has not been clarified yet.

In one study, the use of HS as a chronic therapy for the youngest children with CF, appears to be safe and well-tolerated in most young children with CF (7).

However, the Infant Study of Inhaled Saline (ISIS) (8) failed to achieve a reduction in exacerbations, despite large study numbers, which contrasts with the beneficial effects with HS on exacerbation rate reported in older age groups (4).

In the ISIS study, Rosenfeld and colleagues examined the effectiveness of 48 weeks of twice daily nebulized 7% hypertonic saline, compared with isotonic saline (IS, control), in 321 infants and pre-schoolers (aged less than 6 years) recruited across multiple North American sites. The primary outcome was a reduction in the rate of pulmonary exacerbation, a choice of outcome supported by evidence from a recent study that described correlation between exacerbation rate in the first 2 years of life and lung function outcomes at age 5 years (9).

It is clear that due to these reported ISIS results, benefits seen with HS in older populations cannot be extrapolated at present to management strategies used in younger subjects with CF (10).

However, the smaller ISIS sub studies examining the change in infant lung function measures (plethysmography, forced expiratory flows, and volumes) and multiple-breath washout (MBW) provide interesting insight that functional benefits may yet be proven with HS. In the ISIS infant lung function subgroup (n ¼ 45 infants), only one index demonstrated a statistically significant change (FEV0.5). The potential signal from a physiological test, albeit small in magnitude, is reinforced by the observed changes in the lung clearance index (LCI) with HS presented by Subbarao and colleagues (11). MBW was performed at baseline and at the end of 48 weeks of HS treatment. In this small cohort, the treatment effect of HS did reach statistical significance when LCI was expressed as a z-score change (mean, 2.0 [95% confidence interval, 0.25–3.76]; P ¼ 0.03). The small study numbers and the lack of infants with abnormal LCI at enrolment mean that results should not be over interpreted, but reinforces the exciting potential utility of LCI as an outcome measure recently described in older CF paediatric cohorts, over shorter treatment periods (12, 13).

One recent study (14) opens the discussion on extended use of mucolytics. In this study, children and young adults with CF in the USA had better lung function compared with the UK despite similar nutritional status. This gap was associated with very significant differences in the aggressiveness of care, particularly in CF children, which may have long-term implications to outcome in this disease. They significantly differ from use of hypertonic saline under 18 years of age (US 41% vs UK 8%) and dornase alfa (US 77% vs UK 35%).

Further longitudinal comparisons of national data are needed to unravel the causal implications of earlier and more aggressive treatment of CF children.

These new data on potential benefit of a wide use of hypertonic saline have enhanced the problem of tolerability.

To improve tolerability, some clinicians usually try with lower doses. However, whether patients would still benefit from a lower (but more tolerable) concentration of hypertonic saline is still under debate.

Another approach to the issue of tolerability is to modify the hypertonic saline solution with Hyaluronic acid (HA).

Buonpensiero and colleagues (15) compared the tolerability of hypertonic saline plus HA with that of hypertonic saline alone in patients with CF, treated with one or the other, for 4 weeks. As the primary outcome was to compare HS plus HA with HS in patients who already showed intolerance to HS, endpoints were the symptoms most frequently linked to HS intolerance and poor compliance, i.e., cough, throat irritation, and salty taste. They noted improvements in the tolerability of hypertonic saline and reductions in the perceived salty taste when HA was included in the solution. These changes were both statistically and clinically significant. Furnari et al. (16) confirm these data reporting also a lower rate of use of beta2 bronchodilators.

Another recent study (17) supports this data providing evidence that the association of HA with HS, when given for 28 days, reduces the prevalence and severity of throat irritation, cough, and saltiness, stating that the addition of HA is beneficial in CF patients for whom chronic treatment with HS is indicated and who have previously shown poor tolerance to HS.

It was recently shown that nebulized HA is effective in controlling inflammation *in vivo* in mice CF airways and *in vitro* in human airway epithelial cells. So there will be an additional benefit for the use of inhaled HA as a potential anti-inflammatory medical device in CF therapy (18).

## Conclusion

In conclusion, the use of hypertonic saline is recommended in children (>6y) and adults with CF. For younger children there is good evidence of tolerability and some evidence of efficacy, taking into account the problem of true outcome for this age group. The addition of HA is beneficial in CF patients who have previously shown poor tolerance to HS it may add an important anti-inflammatory effect to this treatment.

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